REMARKS

This paper responds to the Office action in this patent application mailed June 17, 2002. With this amendment, claims 1, 4, and 23-26 are pending. Claims 2, 3 and 5-22 have been canceled. Reconsideration of the present application is respectfully requested in view of the present amendments and remarks.

The applicants petition the Commissioner for a three month extension of time in which to file this amendment. A separate petition for an extension of time is enclosed.

Attached hereto is a marked-up version of the changes made to the title by the current amendment. The attached pages are captioned **"Version with markings to show changes made."**

I. Amendments

A. Amendments to the Specification

Amendments to the specification have been made to reflect the status of the parent application and to correct inadvertent typographical errors. As such, no new matter has been added by these amendments.

B. Amendments to the Claims

Claims 5-9 and 15-22 have been cancelled in accordance with Applicants' election of Group I for prosecution in the present case.[1]

Claim 1 has been amended to recite a polypeptide which is immunoreactive with an antibody that is itself immunoreactive with human prostatic acid phosphatase (PAP) comprising an amino acid sequence presented as SEQ ID NO: 2, including conservative amino acid substitutions that do not alter the sequence by more than 10%. Support for this amendment can be found at page 9, lines 13 to page 10, line 13, Example 3, and claims 1 and 3 as originally filed.

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[1] *See* Paper No. 12.

Claims 2, 3 and 10-13 have been cancelled.

New claims 23-26 have been added. Support for these new claims can be found at page 9, lines 13 to page 10, line 13, Example 3, and claims 10-13, now cancelled.

No new matter has been added by these amendments.

II. Restriction requirement

On April 26, 2002, in response to a restriction requirement imposed by the Examiner on March 26, 2002, Applicants elected the claims of Group I, directed to isolated polypeptides and methods of inducing an immune response against a tumor-associated antigen in a mammalian subject, with traverse, for examination in the present case. In the present Office action, the Examiner has made the restriction final.

Applicants hereby confirm the election of Group I. Non-elected claims 5-9 and 15-22 have been canceled by this amendment.

III. Rejections under 35 U.S.C. § 112

A. Written Description

Claims 1-3 and 12-13 were rejected under Section 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Legal Standard for Written Description

"If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if [not] every nuance of the claims is explicitly described in the specification, then

the adequate written description requirement is met." *See In re Alton*, 76 F.2d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996).

Claim 1

Claims 2, 3, 12 and 13 stand cancelled by this amendment rendering the rejection of these claims moot. Claim 1 remains pending and is amended to describe an isolated polypeptide which is immunoreactive with an antibody that is itself immunoreactive with human PAP and having the amino acid sequence of SEQ ID NO: 2, including conservative amino acid substitutions that do not alter said sequence by more than 10%.

The specification explicitly describes SEQ ID NO: 2, its preparation (Examples 1, 2) and use (Examples 3, 4). Applicants submit that one skilled in the art would understand the inventors to be in possession of polypeptides which are immunoreactive with an antibody that is itself immunoreactive to human PAP which comprise at least 90% sequence identity to SEQ ID NO: 2, *i.e.*, polypeptides which have been conservatively substituted at 1-3 amino acid positions when compared to SEQ ID NO: 2.

For instance, the specification clearly describes six general classes of amino acid sidechains (see page 5, lines 18-20 and page 8, lines 1-3) and provides that minor, substitutions within each class of amino acid sidechains can be made without affecting the antigenic property of SEQ ID NO:2. The resulting polypeptide will contain conservative modifications that do not alter the sequence of SEQ ID NO:2 by more than 10% and is immunoreactive with an antibody that is itself immunoreactive with human PAP.

Thus, Applicants submit that at the time of filing, the inventors had possession of the subject matter of claim 1. Accordingly, withdrawal of the rejection of claim 1 is respectfully requested.

Claim 23

As noted above, new claim 23 finds basis in cancelled claim 13. Claim 23 is directed to a method of inducing an immune response against human prostatic acid phosphatase (PAP) which includes administering an immunogenic dosage of a composition comprising a xenogeneic form of PAP which is immunoreactive with an antibody that is itself immunoreactive with human PAP which has at least 90% sequence identity to SEQ ID NO: 2.

Applicants respectfully submit that the specification adequately describes the method of inducing an immune response of claim 23 so that one skilled in the art would understand that the inventors were in possession of the invention at the time of filing.

The specification discloses methods used to immunize rats with a xenogeneic PAP and methods of evaluating whether a humoral and/or cellular response to the xenogenic PAP took place. *See* page 9, line 10 to page 10, line 12 and Example 3. As stated above with respect to claim 1, the specification clearly describes PAP which is immunoreactive with an antibody that is itself immunoreactive with human PAP which has at least 90% sequence identity to SEQ ID NO: 2. These modified polypeptides can be administered to a subject and the immune response can be measured using the methods disclosed in Example 3 of the specification.

As such, Applicants submit that new claim 23 and claims 24-26 dependent therefrom are adequately described by the disclosure of the specification.

B. Enablement

Claims 1-3 and 12-13 were rejected under Section 112, first paragraph because the specification does not enable one skilled in the art to make/use the invention commensurate in scope with the claims.

Claims 2, 3, 12 and 13 are cancelled by this amendment rendering the rejection of these claims moot.

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[2] *See* Office action at pages 3-4.

As noted above, claim 1 remains pending in amended form and now recites an isolated polypeptide which is immunoreactive with an antibody that is itself immunoreactive with human PAP the amino acid sequence of SEQ ID NO: 2, including conservative substitutions which do not alter the sequence by more than 10%.

New claims 23-26 find basis in canceled claims 10, 11, and 13. Claim 23 is directed to a method of inducing an immune response against human prostatic acid phosphatase (PAP) which includes administering an immunogenic dosage of a composition comprising a xenogeneic form of PAP having at least 90% sequence identity to SEQ ID NO: 2.

Legal standard for Enablement

"'The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.'" *See* MPEP 2164.01, *citing United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

The Examiner's attention is respectfully drawn to M.P.E.P. §2164.01, which outlines the factors to be considered in a determination of undue experimentation, including (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *See also In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Applicants submit that one of ordinary skill in the art in the art can make and use the claimed invention based on the disclosure in the specification without undue experimentation.

With regard to the quantity of experimentation necessary, Applicants point out that, based on the present specification, the quantity of experimentation required to produce a polypeptides which is immunoreactive with an antibody

that is itself immunoreactive with human PAP polypeptide comprising an amino acid sequence of SEQ ID NO:2, including conservative amino acid substitutions which do not alter the sequence by more than 10% is minimal.

As discussed above with regard to written description, the specification describes six classes of amino acids and a skilled artisan would be able to use recombinant methods to make minor, substitutions within each class of amino acid sidechains to produce a polypeptide having at least 90% sequence identity to SEQ ID NO: 2, i.e., having conservative substitutions at 1-3 amino acid positions.

Once the polypeptide is produced, a skilled artisan would be able to use the methods disclosed in Example 3 to determine whether the polypeptide is immunoreactive with an antibody that is itself immunoreactive with human PAP. In Example 3 discloses methods used to immunize rats and mice with purified recombinant mouse PAP and rat PAP, respectively, and methods used to evaluate the antibody titers of the animals using solid phase ELISA assays.

In light of such disclosure, no undue experimentation would be needed for a skilled artisan to confirm whether the xenogenic form of PAP having at least 90% sequence identity exhibits the same antigenic properties as PAP having the sequence of SEQ ID NO: 2.

Thus, the production of a polypeptide having at least 90% sequence identity to SEQ ID NO: 2 and the determination of whether the polypeptide would constitute experimentation which is routine in the art.

With regard to the amount of direction presented, the specification, taken in conjunction with the teachings of the prior art, provide a great deal of guidance as to how to make and use the claimed PAP.

As regards the presence of working examples, the specification contains a number of working examples. For instance, Examples 1 and 2 detail the methods used to prepare SEQ ID NO: 2 and Examples 3 and 4 detail the administration of a xenogenic form of PAP to induce an immune response.

As regards the nature of the invention, the Applicants have discovered that xenogenic tumor-associated antigens can be used to elicit an immune response to the autologous, tumor-associated antigen.

As regards the state of the prior art, the Examiner will agree that a polypeptide which is immunoreactive with an antibody that is itself immunoreactive with human PAP polypeptide comprising an amino acid sequence of SEQ ID NO:2, including conservative amino acid substitutions which do not alter the sequence by more than 10% has not been disclosed in the prior art.

The Examiner will also agree that the relative skill of those in the art is quite high.

The breadth of the claims also supports a finding of enablement. The claims require a polypeptide which is immunoreactive with an antibody that is itself immunoreactive with human PAP polypeptide comprising an amino acid sequence of SEQ ID NO:2, including conservative amino acid substitutions which do not alter the sequence by more than 10% and the use of such PAP to induce an immune response, each of which have been defined appropriately.

As regards the last factor, the predictability here is with respect to retaining antigenicity of a polypeptide which has one or a small number of amino acid substitutions when compared to the sequence of SEQ ID NO: 2. No evidence is presented by the Examiner nor are the Applicants aware of any evidence to suggest that one or a few number of neutral substitutions in a peptide of this length would alter its antigencity. In any case, even if there is a region of critical residues, this area could be easily identified. As such, the level of predictability is reasonable.

Taken in conjunction, a consideration of these eight factors supports a finding of enablement of claim 1 and that claim 1 is commensurate in scope with the teachings in the specification.

Additionally, Applicants urge that to limit the invention as suggested by the Examiner, *i.e.*, to one specific amino sequence, would deprive the Applicants of

the scope commensurate with the contribution made by the inventors. This would occur because if the claims are limited to encompass SEQ ID NO: 2, it would be a simple matter for one skilled in the art to make conservative substitutions to SEQ ID NO: 2 thereby producing polypeptides which exhibit the same antigenic properties but do not read on the claims.

For these reasons, Applicants submit that claim 1, 23 and claims 24-26 dependent therefrom are enabled by the specification and withdrawal of the rejection is respectfully requested.

C. Indefiniteness

Claims 10-13 were rejected under Section 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as the invention. Claims 10-13 have been cancelled, however, new claims 23-26 are supported by claims 10-13 and Applicants wish to address the Examiner's concerns with regard to new claims 23-26.

The Examiner states that claim 10 is indefinite because the preamble of the claim does not state an antigen against which an immune response is raised. The preamble of new claim 23 indicates that human PAP is the antigen against which an immune response is raised.

The Examiner states that claim 12 is indefinite in the recitation of "wherein said mouse PAP is selected according to any of claims 1-4." This claim is cancelled.

The Examiner states that claim 13 is indefinite because there is no antecedent basis for "said xenogenic antigen." Claim 26 depends from claim 23 and includes the limitation that the xenogenic form of PAP is produced in insect cells.

In view of the claim amendments, Applicants submit that the claims comply with the requirements of 112, second paragraph, and withdrawal of the rejection is respectfully requested.

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[3] *See* Office action at page 6.

IV. Rejections under 35 U.S.C. § 102

Claims 1-4 were rejected under 35 U.S.C. § 102(b) as being anticipated by Iype *et al.* (*Arch. Biochem. Biophys.*, 1968, 128(2): 434-441). Claims 2 and 3 are cancelled and Applicants respectfully traverse this rejection with regard to amended claim 1 and claim 4.

Claim 10 was rejected under 35 U.S.C. § 102(b) as being anticipated by Kuciel *et al.* (Biotechnol. Appl. Biochem., 1988, 10(3): 257-272). Claim 10 is cancelled; however, Applicants submit that new claim 23 is not anticipated by Kuciel *et al.* for the reasons detailed below.

A. Applicants' Invention

The invention, as embodied in amended claim 1, is directed to an isolated polypeptide comprising PAP having the polypeptide sequence of SEQ ID NO: 2, including conservative amino acid substitutions which do not alter the sequence by more than 10%.

New claim 23 is supported by claim 10, now cancelled, and is directed to a method of inducing an immune response against human prostatic acid phosphatase (PAP) which includes administering an immunogenic dosage of a composition comprising a xenogeneic form of PAP having at least 90% identity to SEQ ID NO: 2.

B. The Cited Prior Art

1. Iype *et al.* disclose mouse prostate tissue, transformed prostate cells, and epithelial cells of the acini contain acid phosphatase.

Iype et al. do not disclose a mouse PAP having the sequence of SEQ ID NO: 2 or the use of xenogenic form of PAP having the sequence of SEQ ID NO: 2 to induce an immune response in a subject.

2. Kuciel *et al.* disclose the immunization of mice with human PAP to obtain monoclonal antibodies specific for PAP.

Kuciel *et al.* do not disclose a PAP having the sequence of SEQ ID NO: 2 or the administration of a xenogenic form of PAP having the sequence of SEQ ID NO: 2 to elicit an immune response in a mammal.

C. Analysis

For a prior art reference to anticipate in terms of 35 U.S.C. §102, every element of the claimed invention must be identically shown in a single reference. *See Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 7 USPQ 1315 (Fed. Cir. 1988).

None of the cited references teach the elements of the invention as claimed in independent claims 1 and 23.

Claim 1, as amended, is directed to an isolated polypeptide having the sequence of SEQ ID NO: 2. Iype *et al.* do not disclose SEQ ID NO: 2 and as such, an element of claim 1 is not taught by this reference. Thus, claim 1 is not anticipated by Iype *et al.* Claim 4 is dependent upon claim 1 and is not anticipated for the same reasons stated with respect to claim 1.

Claim 23 is directed to a method of inducing an immune response by administering a composition comprising an immunogenic dosage of a xenogenic form of PAP having the sequence of SEQ ID NO: 2. Kuciel *et al.* do not disclose the use of a PAP having the sequence of SEQ ID NO: 2 for use in immunization and as such, an element of claim 23 is not taught by this reference. Thus, claim 23 is not anticipated by Kuciel *et al.*

Accordingly, withdrawal of the rejections under 35 U.S.C. §102 is respectfully requested.

V. Rejection under 35 U.S.C. § 103

Claim 10 was rejected under 35 U.S.C. § 103 over Iype et al., *supra*, in view of Johnstone *et al.* (Immunochemistry in Practice, 1987, 2nd Ed., Blackstone Scientific Publications, Oxford, England, page 30). Claim 10 is cancelled; however, Applicants submit that new claim 23 is not obvious over Iype *et al.* in view of Johnstone *et al.* for the reasons detailed below.

A. Applicants' Invention

New claim 23 is directed to a method of inducing an immune response against human prostatic acid phosphatase (PAP) which includes administering an immunogenic dosage of a composition comprising a xenogeneic form of PAP having at least 90% sequence identity to SEQ ID NO: 2.

B. The Cited Prior Art

1. Iype *et al.* is described above.

2. Johnstone *et al.* disclose methods of producing antibodies which involve "the introduction of immunogen into animals, withdrawal of blood for testing the antibody levels, and finally exsanguination for collection of immune sera." which can used in mice and goats. *See* Section 2.2 of page 30.

Johnstone *et al.* do not disclose a PAP having the sequence of SEQ ID NO: 2, a sequence having at least 90% sequence identity to SEQ ID NO: 2, and do not disclose or suggest the use of xenogenic form of PAP having the sequence of SEQ ID NO: 2 to induce an immune response in a subject.

C. Analysis

According to M.P.E.P. § 2143.03, "to establish a *prima facie* case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. All words in a claim must be considered in judging the patentability of that claim against the prior art." [citations omitted].

Neither Iype *et al.* nor Johnston *et al.* show or suggest a polypeptide having the sequence identified as SEQ ID NO: 2 or a sequence having at least 90% sequence identity to SEQ ID NO: 2. Thus, none of the cited references, either singly or in combination, show or suggest the possibility of using a composition comprising an immunogenic dosage of xenogenic form of PAP having at least 90% sequence identity to SEQ ID NO: 2 to induce an immune response in a subject as claimed in claim 23.

The Examiner asserts that it would have been obvious to induce an immune response using a mouse PAP as disclosed by Iype et al. because once an antigen has been isolated, the manufacture of antibodies against it is *prima facie* obvious.[4] It is further asserted by the Examiner that one of ordinary skill in the art would have been motivated to induce the immune response in a mammal to which the mouse PAP is xenogenic because Johnstone *et al.* teach conventional methods of antibody production and one would have reasonable expectation of success in producing said immune response.[5]

However, Iype *et al.* do not disclose a mouse PAP having at least 90% sequence identity to SEQ ID NO: 2 and as such, the Iype reference fails to teach or suggest an element of claim 23. This lack of disclosure in Iype *et al.* of a PAP having at least 90% sequence identity to SEQ ID NO: 2 is not compensated for by Johnstone *et al.* Nowhere do Johnstone *et al.* disclose a mouse PAP having at least 90% sequence identity to SEQ ID NO: 2 and, in the absence of this, Johnstone *et al.* cannot be said to disclose "a method of inducing an immune response or producing antibodies using a xenogenic form of PAP having at least 90% sequence identity to SEQ ID NO: 2" as presently claimed.

Further, because a PAP having at least 90% sequence identity to SEQ ID NO: 2 is not taught by Iype *et al.* or by Johnstone *et al.*, there is no reasonable expectation of success in producing an immune response as claimed in the method of claim 23.

Accordingly, for the reasons presented above, the method of claim 23 and the claims which depend from it are nonobvious.

VI. Conclusion

In view of the above amendments and remarks, Applicants submit that the claims now pending are in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

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[4] *See* Office action at page 12.
[5] *See* Office action at page 12.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4309.

Respectfully submitted,

Date: 12-17-2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

Please amend paragraph 3 on page 2 as follows:

In a related embodiment, the invention includes the discovery of a novel prostatic acid phosphatase (PAP) polypeptide isolated from mouse, which is xenogeneic with respect to human PAP, and which can therefore be used as an antigen to produce a humoral and/or cellular response against tumor antigens resident in a subject, according to the methods described herein. The isolated PAP polypeptide has at least about 90%, and preferably at least 95% sequence identity to the sequence presented as SEQ ID NO: 2 (mPAP). It is further appreciated that the PAP antigen can be formed [with] by substituting amino acids that represent conservative substitutions for the amino acids of [into] the polypeptide sequence identified as SEQ ID NO: 2 [amino acids that represent conservative substitutions], according to the teachings presented herein.

At line 1 of page 10:

Table [1] 2

In the claims:

Claim 1 has been amended as follows:

1. (amended) An isolated polypeptide which is immunoreactive with an antibody that is itself

immunoreactive with human prostatic acid phosphatase (PAP) comprising [a] an amino acid sequence presented as SEQ ID NO: 2, including conservative amino acid substitutions that do not alter the sequence by more than 10% [having at least 90% sequence identity to SEQ ID NO: 2].

Claims 2, 3, 5-22 have been cancelled.

New claims 23-26 have been added.